American Journal of Medical Genetics 63:46–49 (1996)

Dyssegmental Dysplasia With Glaucoma

Pierre Maroteaux, Sylvie Manouvrier, Jacky Bonaventure, and Martine Le Merrer

Unité de Recherches sur les Handicaps Génétiques de l'Enfant, INSERM U 393, Hôpital des Enfants Malades, Paris (P.M., J.B., M.L.M.), and Services de Pédiatrie et de Génétique Médicale, Hôpital Huriez, Lille (S.M.), France

We report on a "new" syndrome in 2 unrelated children with some manifestations of Kniest dysplasia and with spine abnormalities suggestive of dyssegmental dysplasia. Glaucoma with important ocular impairment was associated with severe dwarfism. No mutation of the COL2A1 gene was detected. The inheritance of this new type of skeletal dysplasia is unknown.

KEY WORDS: Kniest dysplasia, dyssegmental dysplasia, glaucoma, coronal cleft of vertebral bodies

INTRODUCTION

Kniest dysplasia [Kniest, 1979; Maroteaux and Spranger, 1973] is a well-known rare disorder recognized at birth by dwarfism, enlarged knees, flat face with prominent eyes, and severe myopia. It is an autosomal dominant condition due to COL2A1 mutations [Winterpacht et al., 1993].

A sublethal dwarfism resembling Kniest dysplasia with specific vertebral changes of spine was described by Gruhn et al. [1978] and is called dyssegmental dysplasia. The inheritance of this condition is autosomal recessive. The molecular defect remains unknown [Handmaker et al., 1977; Gruhn et al., 1978].

Here, we report on 2 unrelated children, male and female, with severe micromelia and findings of Kniest disease and dyssegmental dysplasia associated with severe ocular impairment.

CLINICAL REPORTS

Patient 1

This girl was born to nonconsanguineous and unaffected parents after an uncomplicated pregnancy. However, short limbs were noted by echographic survey at 6 months of gestation.

At birth, dwarfism was obvious, with a length of 40.5 cm, and obvious exophthalmia was detected due to severe glaucoma. The skull was dolichocephalic, with very large anterior fontanel, flat face, and cleft palate (Fig. 1a). Large articulations were limited and the knees seemed to be enlarged. Hands were normal.

Roentgenograms showed, at birth, short and stubby long bones with flared metaphyses, retarded ossified epiphyses, and flat vertebral bodies. A cleft of the first sacral vertebral body and coronal notches on lumbar vertebrae were present. Chromosomes were normal (46,XX).

Follow-up examination showed severe ocular impairment due to glaucoma and corneal opacities, deafness, and motor delay. Dwarfism was severe (height, 81 cm at age 8 years) and movements of joints were limited (elbow, hip). Radiographic findings showed flaring of metaphyses, with very short long bones (Fig. 2a), enlarged epiphyses at the knees, and absence of development of the capital femoral head. Vertebral bodies were irregular, flattened, and enlarged (Fig. 3a). The pelvis was hypoplastic, with rounded iliac wings.

Molecular analysis was performed on the COL2A1 gene by the single-strand conformation polymorphism method, and no mutation was detected.

Patient 2

This boy was the firstborn of nonconsanguineous, healthy parents. At 6 months of fetal life, ultrasonography documented short limbs, and depressed nasal root on fetal face profile with deformed skull. Fetal karyotype was normal. Radiographic examination was performed in utero and did not show severe modification of long bones, but clefts of the lumbar spine were detected. Craniosynostosis was suspected, but the pregnancy was continued.

At birth, the boy was short, with length of 47 cm, and weight of 3,400 g. We also noted a flat face, frontal bossing, large fontanel, severe exophthalmia, "retracted" midface with depressed nasal bridge, and short nose (Fig. 1b). Elbow movements were restricted, but hands and feet seemed to be normal; rather than a cleft palate, there was a high-arched palate.

Radiographs showed short, stubby, bowed long bones with large and flared metaphyses (Fig. 2b). Ossification of the skull was incomplete; in the spine, vertebral bodies were irregular with slight platyspondyly and coronal cleft in the lumbar region (Fig. 3b).

Received for publication February 8, 1996; revision received February 9, 1996.

Address reprint requests to Dr. Martine Le Merrer, Unité de Recherches sur les Handicaps Génétiques de l'Enfant, INSERM U393, Hopital des Enfants Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

Fig. 1. **a:** Patient 1, age 1 year. Note exophthalmia and short limbs. **b:** Patient 2, at birth. Note severe exophthalmia with dolichocephalic skull.

Ophthalmological examination showed severe glaucoma due to iridocorneal dysgenesis.

At age 6 months, the patient's length was 64 cm and motor development seemed to be delayed, but he smiled and noted objects. Visual impairment seemed to be moderate. CT scan was normal. His hearing appeared to be normal.

DISCUSSION

We report on 2 children with some manifestations of Kniest dysplasia, which is characterized by facial changes, cleft palate, and deafness. X-ray findings included short and stubby long bones with flared and slight irregular metaphyses, and flat vertebral bodies.

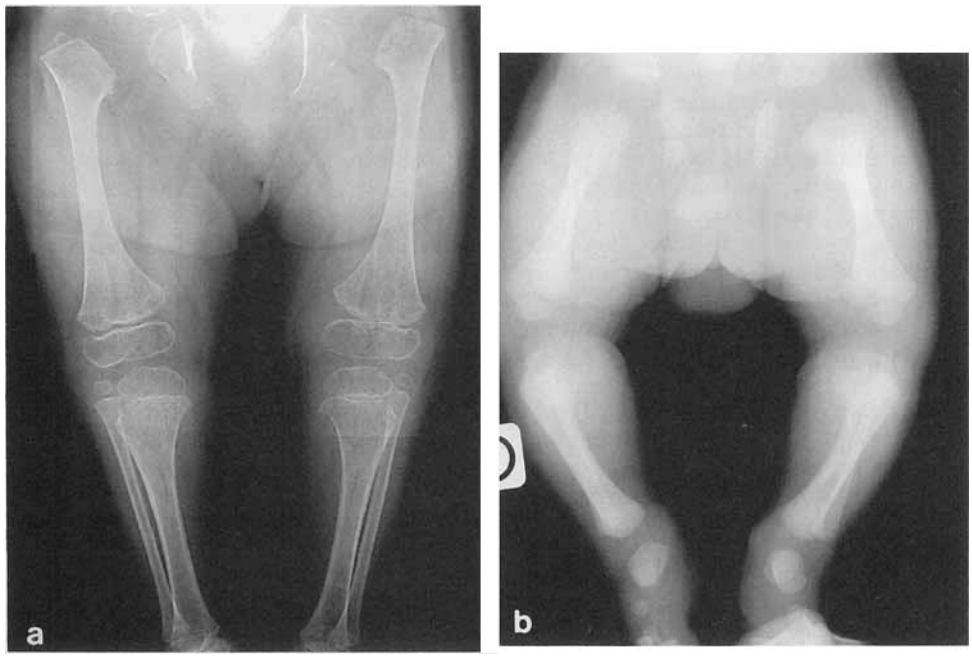

Fig. 2. **(a)** Patient 1 and **(b)** patient 2, lower limbs. Note shortness of long bones, enlarged femoral and tibial epiphyses at knees, and unossified capital femoral head.

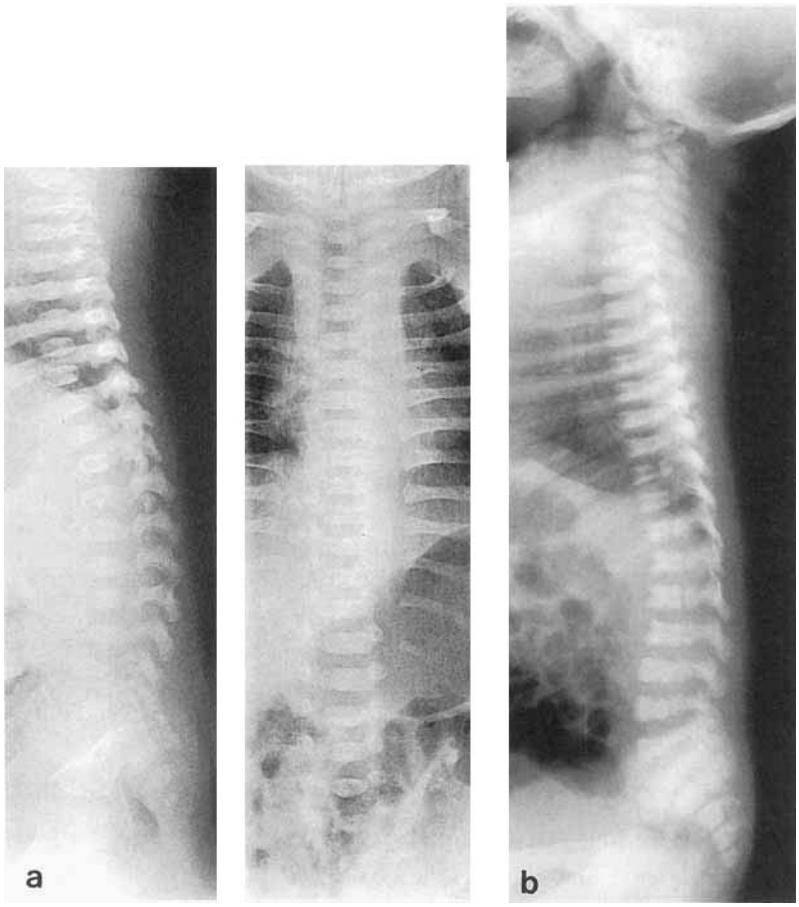

Fig. 3. **a:** Patient 1. Lateral view of spine. Note platyspondyly and cleft of sacral vertebral bodies. **b:** Patient 2. Note coronal cleft of lumbar vertebral bodies.

Further epiphyseal changes included enlarged epiphyses of the knee, whereas the capital femoral heads remained unossified throughout childhood.

Nevertheless, vertebral abnormalities such as irregular and cleft vertebral bodies, and the defects of skull ossification present in the 2 patients, support the diagnosis of dyssegmental dysplasia. In this condition, severe micromelia with bowing of long bones, flat face with depressed nasal root, microretrognathia, and cleft palate are the main clinical findings. On roentgenographs, shortness and bowing of long bones, flaring of metaphyses, platyspondyly, and coronal cleft of lumbar vertebral bodies are among specific changes. This dysplasia appears to represent a heterogeneous group of disorders with at least two distinct forms [Aleck et al., 1987]. The Silverman-Handmaker type is the more severe form, lethal soon after birth, with severe segmentation defects of the entire spine, and shortness of limbs with midshaft angulation [Handmaker et al., 1977; Fasanelli et al., 1985; Stöß, 1985]. Encephalocele and other central nervous system abnormalities are frequent. The Rolland-Desbuquois type is milder, with specific vertebral findings such as coronal cleft and binucleation of lumbar vertebral bodies [Rolland et al., 1972; Bueno et al., 1984; Andersen et al., 1988]. Dwarfism and micromelia are less severe, and survival is longer.

In our 2 cases, the radiological changes of the lower limbs suggest Kniest dysplasia, whereas the vertebral defects are in favor of dyssegmental dysplasia, type II. Nevertheless, in Kniest dysplasia ocular findings are characterized by severe myopia with frequent retinal detachment, but congenital glaucoma is not usual, whereas in dyssegmental dysplasia, ocular abnormalities are absent.

The severity of dwarfism, and the clinical and radiological findings, associated with glaucoma in 2 unrelated children, allow us to delineate a new entity. No deletion or mutation in the COL2A1 gene was found in patient 1, suggesting that the diagnosis of Kniest dysplasia is unlikely. The inheritance of this syndrome remains unclear, because these cases were sporadic, without consanguinity.

REFERENCES

Aleck KA, Grix A, Clericuzio C, Kaplan P, Adomian GE, Lachman R, Rimoin DL (1987): Dyssegmental dysplasias: Clinical, radiographic, and morphologic evidence of heterogeneity. Am J Med Genet 27: 295–312.

Andersen PE, Hauge M, Bang J (1988): Dyssegmental dysplasia in siblings: Prenatal ultrasonic diagnosis. Skeletal Radiol 17:29–31.

Bueno M, Argemi J, Maroteaux P (1984): Dysplasie dyssegmentaire: À propos de 2 cas familiaux d'évolution létale. Arch Fr Pediatr 41: 269–271.

Fasanelli S, Kozlowski K, Relter S, Sillence D (1985): Dyssegmental dysplasia (report of two cases with a review of the literature). Skeletal Radiol 14:173–177.

Gruhn JG, Gorlin GJ, Langer LO (1978): Dyssegmental dwarfism: A lethal anisospondylic camptomicromelic dwarfism. Am J Dis Child 132:382–386.

Handmaker SD, Campbell JA, Robinson LD, Chinwah O, Gorlin JG (1977): Dyssegmental Dwarfism: A New Syndrome of Lethal Dwarfism. BD:OAS XII (3D):79–90.

Kniest W (1979): Das Kniest-Syndrome and seine Differentialdiagnose. Dtsch Gesundh 34:1317–1321.

Maroteaux P, Spranger J (1973): La maladie de Kniest. Arch Fr Pédiatr 30:735–750.

Rolland JC, Laugier J, Grenier B, Desbuquois G (1972): Nanisme chondrodystrophique et division palatine chez un nouveau-né. Ann Pediatr (Paris) 19:139–143.

Stöß H (1985): Dyssegmentaldysplasie. Fallbeschreibung und Literaturübersicht. Pathologe 6:88–95.

Winterpacht A, Hillert M, Schwarze U, Mundlos S, Spranger J, Zabel BU (1993): Kniest and Stickler dysplasia phenotypes caused by collagen type II gene (COL2A1) defect. Nat Genet 3:323–326.